Response

Claims 94-110, 112-113, and 115-116 are currently pending and under examination. Claims 94, 96, 104, 107-108, and 112-113 have been amended to more clearly define Applicants' invention. The content of claims 105 and 106 is now contained in other claims, and claims 105 and 106 are cancelled.

Support may be found for the amendments to claims 94 and 108 as follows. The use of "therapeutic agents" and the administration of "therapeutically effective amounts" are found at least at page 18, line 32 through page 19, line 13 in support of the claimed phrase "therapeutically regulating." The term "selectively inhibiting" by the administered NHE inhibitor is found at least at page 5, lines 25-26 and at page 26, line 20.

The function of the NHE inhibitor as a "selective inhibitor" at "low concentrations functions" is supported at least at page 5, lines 20-21 and 29-30 ("selectively blocked in glaucomatous patients by specifically inhibiting NHE-1 with low concentrations at very low concentrations . . . low dosages permit the drugs to be used without any, or with minimal adverse side-effects") and in the Abstract ("This discovery is particularly relevant because of the known sensitivity of the exchanger to a number of modulating drugs or compounds, which are effective at very low concentrations"). The "inhibitor constant (Ki)" of the administered NHE inhibitor is supported at least at page 13, line 29 through page 14, line 3, and at page 28, lines 20-24 (Ki is a function of inhibitor concentration). The values of Ki are specific to the interaction between one type of sodium-hydrogen exchanger and one inhibitor. The sodium-hydrogen exchanger NHE-1 is the most sensitive of the NHEs to inhibition by the amiloride analogues. Page 33, lines 4-5 discuss that the "values obtained for Ki are uniquely characteristic of NHE-1 among the family of known isoforms of the Na+/H+ antiport." To determine the functional effectiveness of the inhibitor, Applicants measured sodium uptake by pigmented ciliary epithelial cells in exchange for hydrogen ions. See Figure 9. Support for the phrase "characteristic of NHE-1 antiport blockers" is further found at page 6, lines 26-29 ("Modulators of the antiports are . . . . at concentrations characteristic of the NHE-1 isoform").

"Regulating aqueous humor formation" is supported at page 6, line 26; page 11, lines 10-11; page 14, line 25, etc. "Reducing net inflow" is described by a combination of the following: "reducing net secretion" is found at page 2, lines 1-2; "lowering . . .

aqueous humor inflow" is found at page 4, lines 8-9; "net uptake" is found at least at page 12, line 8, and "fluid uptake . . . inhibited" and "net fluid uptake" is found at page 16, lines 7-11, etc.

In claim 104, the terms "elevated intraocular pressure" and "low intraocular pressure" as used in the claim are found on page 10, in the first paragraph of the Description.

The use of amiloride "analogues," rather than "derivatives," is supported at least at page 15, line 3 and at Table 5. The change in claim 113 is supported by claim 107. Applicants have elected to remove "amiloride" per se from the claims as less effective, but continue to claim "amiloride analogues." No new matter was added by any amendment.

Response to Claim Rejection under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claims 101 and 115-116 under 35 U.S.C. §112, first paragraph, under the written description requirement regarding Applicants' use of the term "precursor prostaglandins." In making this rejection, the Examiner appears to question whether Applicants have presented any prostaglandin precursor other than latanoprost. See Applicants' specification at page 3, lines 27-28. Also please note that Applicants claim only "at least one compound selected from the group consisting of . . . .a precursor prostaglandins." Latanoprost exemplifies "at least one compound" from the group . . . .precursor prostaglandins, thus satisfying the requirement under the law.

It is well settled that while the purpose of §112, first paragraph, is to ensure that there is an adequate disclosure of the invention for which patent rights are sought and the purpose of the description requirement is to state what is needed to fulfill the enablement criteria, these requirements may be viewed separately but they are intertwined. *Kennecott Corp. v. Kyocera International, Inc.*, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987) ("The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention.")

Turning to the statement from Applicants' specification quoting the use of a prostaglandin precursor, refers to latanoprost at page 3, lines 15 – 28 as "another new type of drug . . . are also in current use." One of ordinary skill in the art would therefore, as part of his/her full knowledge, be familiar with such drugs if they are in current use, and would know which drugs are being referred to as a prostaglandin precursor for the stated purpose.

Applicants have extended the definition of which drugs are intended by *exemplifying* latanoprost. Nowhere, however, do Applicants limit the claimed pharmaceutical composition to *only* latanoprost, nor are they so required by the law.

The courts have explained that "adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention. Rather, it is sufficient if the originally-filed disclosure would have conveyed to one of ordinary skill in the art that the appellant had possession of the concept of what is claimed." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (BPAI 1993). Since the purpose of the law is to provide satisfaction of the description requirement to insure that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application, Applicants have met this goal by not only providing the class of compositions referred to, but also an example of a member of the class known to the skilled practitioner. Multiple examples are not needed to exemplify the prostaglandins precursor drugs as a class in light of the lantanoprost example.

> It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. "A specification may, within the meaning 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses." *Utter v. Hiraga* 6 USPQ2d 1709, 1714 (Fed. Cir. 1988). "Representative samples are not required by the statute and are not an end in themselves." *In re Robbins*, 166 USPQ 552, 555 (CCPA 1970). *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

As further explained by the court in *In re Metcalfe*, 161 USPQ 789 (CCPA 1969), "under appropriate circumstances an applicant may describe a material used in a claimed invention by referencing materials sold under a particular trade name or trademark." In this case, Applicants have exemplified one of a class of prostaglandins precursor drugs "currently in use," by naming an example from the identified group – namely latanoprost. Thus, Applicants have met the written description requirement by identifying the prostaglandins precursor drugs as those which would be readily recognized by the intended practitioner.

Accordingly, Applicants respectfully ask that the 112 rejection be reconsidered and withdrawn.

Response to First Rejection under 35 U.S.C. §102(b) over Cherksey

The Examiner has rejected claims 94-96, 102 and 105-107 under 35 U.S.C. §102(b) as anticipated by Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner relies upon Cherksey for the teaching that amiloride is an agent that "blocks ion transport and interacts with a Sodium-Hydrogen Exchange inhibitor," and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. See columns 1-3. This conclusion is incorrect, as will be shown. Cherksey does not actually teach any interaction with a "sodium-hydrogen exchange inhibitor," nor is the amiloride gel utilized by Cherksey at pH 4.5 suitable for actual administration to the eye.

The formation of the aqueous humor of the eye is defined and explained in the first paragraph of Applicants' invention, as well as in the many references on the subject that Applicants have already placed into the record. The formation of the aqueous humor requires active metabolism occurring the double-layered ciliary epithelium, *i.e.*, two layers of cells whose apical membranes are juxtaposed (see Applicants' FIG. 1). The apex to apex positioning of the secretory epithelia is unusual. Thus, there is a layer of the outer pigmented epithelium (PE), with its basement membrane resting on the ciliary stroma, and the inner nonpigmented epithelium (NPE), with its basement membrane facing the posterior chamber. The secretion is based on the movement of water and electrolytes from the ciliary stroma across the epithelial cell layer, and into the posterior chamber, where they are secreted at the basolateral membrane as aqueous humor. See, Civan and Macknight, "The ins and outs of aqueous humour secretion," *Experimental Eye Research* 78(3):625-631 (March 2004).

The secretion proceeds in three steps: stromal chloride entry into pigmented cells, diffusion through gap junctions and final non-pigmented cell secretion. At the stromal surface, swelling-and cyclic adenosine monophosphate-activated maxi-chloride channels can recycle chloride, reducing net chloride secretion. While at the aqueous-humor surface, swelling- and A3 adenosine receptor-activated chloride channels subserve chloride release into the aqueous humor. See, Do and Civan, "Swelling-activated chloride channels in aqueous humour formation: on the one side and the other," *Acta Physiologica* 187(1-2): 345-352 (May/June 2006).

The epithelial sodium channel referred to by Cherksey is not shown in Applicants' FIG. 1, since the sodium channel is not a significant contributor to net formation of the aqueous humor, and because it is found in the NPE cell layer facing the aqueous humor, it falls outside of Applicants' invention which is limited to inhibition of the sodium-hydrogen antiports (or exchangers). The ciliary epithelial cell antiports are also known as exchangers or counter-transporters. The antiports of the present invention (FIG. 1) are the paired sodium-hydrogen (Na^+/H^+) and $Cl^-/HCO3^-$ antiports (or exchangers) in the pigmented epithelial (PE) cell layer. The formation of aqueous humor occurs as Na^+ enters the PE cells from the body side, and, in exchange, hydrogen ion (H^+) is released from the cell onto the body side.

As noted in Applicants' background of the invention, there are multiple interacting causes of increased intraocular pressure, and affecting the general process using non-selective inhibitors has been known in the art. But such therapies cannot be controlled and the eye is placed at risk by high doses of agents over long periods of time in an often ineffective effort to reduce intraocular pressure. The goal of medicine in general is to provide therapeutic treatment to a patient that offers the optimal result while causing the least amount of harm or side effect. This is accomplished by controlled measures and selective timing or administration.

Applicants administer an NHE inhibitor for the "selective inhibition" of the sodium-hydrogen antiports, which permits the precise and exact treatment of the antiports to inhibit aqueous humor formation and reduce net inflow. The term "selective inhibitor" in independent claims 94 and 108 distinguishes Applicants' invention from the prior art, because while other agents may result in diminished intraocular pressure by acting on the general fluid transport process, none selectively inhibit the sodium-hydrogen antiports in the eye. As a result, the prior art cannot achieve the "selected" inhibition of aqueous humor formation and net inflow achieved by Applicants. There is no evidence that the cited prior art offers selective inhibition of the sodium-hydrogen antiports, or that, in fact, Cherksey's method operates on the sodium-hydrogen antiports at all since there are many components to the control of intraocular pressure. Without evidence that Cherksey's gel would necessarily offer Applicants' defined selective inhibition, such a selective effect is not, and cannot be assumed to be, inherent in the Cherksey reference.

In response to the Examiner's conclusions, Applicants point out that Cherksey's patent is actually very narrow, dealing with a peptide isolated from normal membranes that he found conformed to amiloride-sensitive channels. It is known that amiloride blocks the sodium channel – but that requires an understanding that the sodium channel is not the same as or equivalent to the sodium-hydrogen antiport. The sodium channel and the sodium-hydrogen antiports as explained above – are not even found in the same regions of the epithelial cells of the eye. In fact, Merck developed amiloride for the purpose of blocking the sodium channel. However, while Cherksey claims the use of amiloride solely for the use of the isolated peptide as a diagnostic and experimental tool, whereas by comparison, Applicants' invention neither teaches, nor claims, a method for regulating the "sodium channel" or its role in aqueous humor formation. Cherksey's method of binding amiloride in affinity gels would affect only the sodium channels (including amiloride-sensitive NPE sodium channels) that underlie *reabsorption* of aqueous humor fluid – not the formation of the aqueous humor, meaning that by definition the Cherksey teachings fall outside of Applicants' invention.

Cherksey states an "understanding"at col. 1, lines 24-27 as background for his invention that "Amiloride is widely thought to interact with a Na^+/H^+ exchanger [antiport] at high concentrations and a Na^+ channel protein at much lower concentrations." By this statement Cherksey was distinguishing his work to find low concentrations of amiloride to test for sodium channels using affinity gels in a laboratory setting, from any effect on the sodium-hydrogen channels, which he knew would require much higher, in fact dangerously high, concentrations of amiloride. The basis for Cherksey's statement was solubility. The limited solubility of amiloride remained a problem ten years after Cherksey's patent, and is the reason that Avila *et al.*, "Inhibitors of NHE-1 Na^+/H^+ exchange reduce mouse intraocular pressure," *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902 (2002) (previously cited in Applicants' record, not as prior art, but establish the state of the art) included the solvent DMSO (dimethylsulfoxide), see page 1899, paragraph 3. But even then, 10 mm concentrations of amiloride at the eye surface had no effect on intraocular pressure, presumably because the concentration reaching the NHE target was much lower. While there are pharmaceutical ways of increasing solubility, none have as yet been developed for amiloride.

The values of Ki are specific to the interaction between one type of sodium-hydrogen exchanger and one NHE inhibitor. Calculation of these values of Ki is straightforward to one skilled in the art as presented in Applicants' specification at page 13, line 29 through page 14, line 3, and at page 28, lines 20-24 and page 33, lines 4-5 As shown in Applicants' Figure 9 the open triangles show that the fractional uptake of sodium (Na) is reduced to about 30% of its control level when the logarithm of, *e.g.*, the EIPA concentration is more negative than -1. For EIPA, as an example, this logarithmic value corresponds to 0.068 micromolar (μM). See calculated values presented in Table 5 The logarithmic value needed for amiloride (filled diamonds) to inhibit sodium-hydrogen exchange is much larger (shifted to a positive logarithmic value on the right), and corresponding to about 4 micromolar (μM). However, since Applicants' intent was to selectively use an NHE inhibitor that blocks *sodium-hydrogen exchange* (antiport) at the lowest possible concentration to avoid side effects (see page 11, line 18), so that the effects of an inhibitor, *e.g.*, EIPA, will not affect other proteins (such as the *sodium channe*l target of Cherksey) which would otherwise require very high concentrations of the compounds used to affect the *sodium channel.*

Thus Cherksey teaches that blocking the sodium channel with amiloride *increases* inflow, *resulting in increased intraocular pressure* – which is contrary to the clinical intent of Applicants' invention. On the basis of that information, a knowledgeable practitioner would be led to *stimulate* the NPE sodium channels; not block them, and further demonstrates that Cherksey's invention to determine the effect of amiloride on the sodium channels would have had no effect, particularly at the concentrations used by Cherksey, on the sodium-hydrogen antiports that are selectively inhibited by Applicants' claimed method. Thus, Cherksey not only fails to anticipate Applicants' invention, it actually leads one away from what is taught by Applicants' patent application regarding regulation of the antiports.

Moreover, Cherksey's speculation that amiloride-sensitive channels could be inhibited in dealing with many diseases, including glaucoma is unsupported and not enabled by the cited patent which teaches only methods relating to sodium channels. No evidence, let alone a rationale basis, is provided in the cited patent or anywhere in the prior art for such speculation, and others could not be taught by a mere speculation. More

importantly, Cherksey neither mentions, nor suggests, that inhibiting or blocking NHE exchange would reduce aqueous humor inflow or intraocular pressure. Thus, although Cherksey, as a valid patent, may be admitted for all that it teaches, it can at best be considered valid only for the use of amiloride, and at that only for the effect on sodium channels, it cannot be considered valid for that which it fails to encompass. Accordingly, Cherksey fails to anticipate each and every element of Applicants' claimed invention - which requires "selective inhibition of the sodium-hydrogen antiports" by the administration of a selective inhibitor – the NHE inhibitor. As a result, the Cherksey reference fails to anticipate Applicants' present invention.

Applicants ask that in light of the arguments and evidence of record, and of the amended claims, the rejection of Applicants' claims under 35 U.S.C. §102(b) over Cherksey be reconsidered and withdrawn, and the case moved to allowance.

Response to Second Rejection under 35 U.S.C. §102(b) over Drug Facts and Comparisons

The Examiner has rejected claims 94 and 102-105 under 35 U.S.C. §102(b) as being unpatentable under "Drug Facts and Comparisons" (1994). In making this rejection, the Examiner relies upon "Drug Facts and Comparisons" for teaching the use of timolol, which the Examiner defines as a beta blocker in reliance on the prior art and on Applicants' list at page 6, lines 23-26. However, as previously shown on the record, by cited prior art and by Declaration in Applicants' prior Response dated November 10, 2005, timolol was not recognized by those knowledgeable in the field to be a sodium-hydrogen exchange (NHE) inhibitor.

Regardless of the Examiner's arguments that reduction of intraocular pressure is demonstrated by the use of timolol in "Drug Facts and Comparisons," the reference offers no evidence that timolol achieved any inhibition of sodium-hydrogen antiport activity *in the ciliary epithelial cells.* It describes a change in intraocular pressure, not any effect what-so-ever on the ciliary epithelial cells. In fact, the effect of any pharmaceutical composition on the antiports and the effect of such treatment were unknown until its discovery by the present inventors, so it could not have been known or suggested by the art. As a result, nowhere in the prior art is there a suggestion that the antiports controlled fluid build up in the aqueous humor, and nowhere is there a suggestion that the NHE

inhibitors could control the activity of the antiports. Yet, that is what is claimed by Applicants - not simply a possible effect on intraocular pressure.

Applicants not only "administer" a pharmaceutical composition in their claimed method, the composition is expressly an NHE inhibitor that "selectively" inhibits "sodium-hydrogen antiport activity" in the ciliary epithelial cells. This further emphasizes that, while "Drug Facts and Comparisons" may say that a small reduction of intraocular pressure was noted in the subject animal, the cited art does not offer any treatments of antiport activity – yet regulating antiport activity is expressly Applicant's invention – not simply reducing intraocular pressure.

This is not a case of inherency because while "Drug Facts and Comparisons" may report a reduction of intraocular pressure in the subject animal in conjunction with treatment, there is no evidence provided in the rejection that would indicate that the noted slight reduction was *a selective result of inhibition or regulation of antiport activity* or that the epithelial cells were even affected. The cited reference offers no suggestion that intraocular pressure was tested by the authors of "Drug Facts and Comparisons."

In citing *Continental Can*, the Office must look at the entire holding of the decision, which further explains that

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA Inc. v. Monsanto,* 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

It cannot be assumed, without some evidence supporting the conclusion that the treatment by the authors of "Drug Facts and Comparisons" "could" have regulated or altered the antiport activity, or that such action on the antiports was inherent based upon the limited disclosure in the cited reference. Only Applicants' own invention could lead to the conclusion that the treatment described in "Drug Facts and Comparisons," but of course, such reliance is not permissible for finding anticipation (inherently or otherwise).

However, the Examiner also refers to the use of timolol in "Drug Facts and Comparisons" as "a protective utility," and states that limitations from the specification cannot be read into the claims. More specifically the Examiner refers to "Applicants'

failure to distance the proffered claims from the anticipated **prophylactic** utility" of the cited reference. Applicants appreciate the suggested differentiation from the cited reference, and point to the existing language in each of the independent claims (upon which all remaining claims depend) that establishes that the NHE inhibitor is administered to the cells of a patient in need of the identified inhibitory regulation. In other words if the patient is already in need of the identified inhibition, the administration is necessarily therapeutic, rather than prophylactic, since *prophylactic* administration would be, by common definition, *before* the onset of symptoms, *i.e.*, before the need arises. *Therapeutic* administration would *follow onset* of the need. Accordingly, Applicants' invention is necessarily therapeutic rather than prophylactic as stated in the independent claims. Nevertheless, to advance allowance of the claims and to make the fact that the invention is a therapeutic method, the independent claims have been amended to specify that the claimed method is "for therapeutically regulating intraocular pressure by selectively inhibiting sodium-hydrogen antiport activity."

Consequently since each and every element of Applicants' claims 94 and 108, and the cited claims dependent thereon, are not expressly or inherently described in a single prior art reference, Applicants' claims are not anticipated under 35 U.S.C. § 102(b). See, e.g., *Verdegaal Brothers, Inc. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) ("Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.).

As a result, Applicants ask that in light of the claim amendments, the arguments of record and the foregoing arguments, that the rejection under 35 U.S.C. § 102(b) over "Drug Facts and Comparisons" be reconsidered and withdrawn, and the case moved to allowance.

Response to Rejections under 35 U.S.C. §103(a) over Adorante and Cherksey

The Examiner has rejected claims 94-96, and [99-113] 99 – 110, 112, 113 under 35 U.S.C. §103(a) as unpatentable over Adorante (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591). Note, please that claim 111 was previously cancelled in the record, and cannot be subject to further rejection. In making this rejection, the Examiner relies on Adorante for the use of 4,4'-diisothiocyanato-stilbene-2,2'-disulfonate (DIDS) to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Adorante

fails to suggest co-administration of NHE/NHE1 inhibitors. However, the Examiner further combines Cherksey with Adorante for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition." However, Applicants refute the Examiner's conclusion.

Before understanding the effect of the combined references, one must first understand what is contributed by each of the cited references to the combination. Contrary to the Examiner's conclusion, Adorante actually proposes the use of DIDS as a chloride-channel blocker of NPE cells, without any reference what-so-ever to bicarbonate-chloride exchange. The chloride channel is not even shown in Applicants' Figure 1 - because it is not part of Applicants' invention. Only inhibition of, and within, the NPE cells is claimed in Applicants' invention. Applicants do not say that the chloride channels may not be involved in the intraocular pressure; they state only that the use of DIDS as a chloride-channel blocker is not their invention, even if DIDS may also be effective as an NHE inhibitor. However, Adorante's treatment of the chloride channels is unrelated to Applicants' invention, which requires the administration of a selective NHE inhibitor.

To meet this deficit, the Examiner relies upon the above described Cherksey reference to supply the NHE inhibitor element of Applicants' invention when Adorante is combined with Cherksey. However, for the reasons discussed in Applicants' Response to the 102(b) rejection over Cherksey (above), the Cherksey method may suggest a treatment by formulating an amiloride-based gel to test effects on the *sodium channels* of the eye - if pH 4.5 agents could be used without harming the eye - but it offers no administration of a selective NHE inhibitor to the ciliary epithelial cells of the eye to selectively regulate the sodium-hydrogen antiports which are found in an entirely different region of the epithelia of the eye. Cherksey is not distinguished in Applicants' specification because Applicants' invention offers no discussion at all of the role of the "sodium channels" that Cherksey addresses and their role in aqueous humor formation. While Applicants' do not claim to control *all* of the mechanisms involved in increased intraocular pressure, the art clearly

recognizes the existence of multiple factors and mechanisms involved in the causes and treatments of intraocular pressure. If Cherksey's discussion of the sodium channels are indeed a potential treatment of glaucoma, as suggested by the Cherksey reference, they are neither inherent in nor suggestive of the selective NHE regulatory mechanisms presently claimed by Applicants.

For the Examiner to assume that because Cherksey and Adorante have documented the use of certain agents that appear to have altered, or could affect intraocularpressure is in no way a suggestion that they have identified all of the involved mechanisms, or that the regulations using selective NHE inhibitors that control only the NHE transport *within* and between the cited epithelial cells in Applicants' claimed methods are suggested by, or inherent in, the combined prior art. There are clearly multiple major ionic mechanisms operating as a cause of unwanted increases in intraocular pressure in addition to chloride secretion or the sodium channels – both of which lie outside of the region of sodium-hydrogen transport controlled by the selective inhibition of Applicants' claimed method. Thus, to preclude inventions that address the other avenues involved in aqueous humor regulation, would impermissibly block future advances in the science.

Whatever effect Cherksey's amiloride gel composition may have on glaucoma, not that Applicants' agree that it would have any effect except damage to the eye, can only be assumed to have resulted from the method and compositions disclosed in the Cherksey patent specification, which by Cherksey's own definition (see arguments in response to the 102(b) rejection) operates in a manner that is independent of Applicants' invention. In fact, as explained above, even when applied in combination with Adorante, Cherksey actually teaches away from Applicants' invention because together they define actions only on regions of the eye outside of the transport between and within the pigmented and non-pigmented ciliary epithelial cells, and Cherksey's material is ineffective in Applicants' invention. Moreover, the inherency argument used to support the use of Cherksey under the 102(b) is inapplicable for the combined 103 rejection. See, *Jones v. Hardy* 220 USPQ 1020, 1025 (Fed. Cir. 1984) (The fact that a claimed invention is based on an inherent quality of a product well known in the art does not mean the invention is obvious as this confuses anticipation by inherency with obviousness).

Consequently, linking DIDS that blocks chloride channels (Adorante) with amiloride affinity gels at pH 4.5 to measure effects on the ENaC sodium channel (Cherksey) on the outer side of the epithelial cells, would in no way lead one of skill in the art to believe that such a combination would lead to the selective blocking of sodium-proton exchange in order to reduce inflow at the ciliary cell antiports in accordance with the method claimed by Applicants. Even when combined, the cited references fail to teach each and every element of Applicants' claimed invention.

Since Cherksey fails to teach administering selective NHE/NHE1 inhibitors to the antiports, it cannot supplement the gap left by Adorante; and alone, Adorante cannot render Applicants' invention obvious. Accordingly, although combined, the cited references fail to render Applicants' claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 94-96, and 99-110, 112, 113 under 35 U.S.C. §103(a) be reconsidered and reversed, and the case move to allowance.

Response to Rejections under 35 U.S.C. §103(a) over Brandt and Cherksey

The Examiner has rejected claims 94-98, and [102-113] 102 – 110, 112, 113 under 35 U.S.C. §103(a) as unpatentable over Brandt (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591). Please note that as above claim 111 has been previously cancelled and cannot now be rejected. In making this rejection, the Examiner relies on Brandt for the use of an inhibitor of a Na^+-K^+-$2Cl^-$ (symport), such as bumetanide, to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Brandt fails to suggest co-administration of NHE/NHE1 inhibitors. However, the Examiner further combines Cherksey with Brandt for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor, and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition." Applicants, however, refute the Examiner's conclusion.

Contrary to the Examiner's position, Applicants point out there are many different components recognized in the prior art to control intraocular pressure, and the identification of a method in the prior art that affects one part of this complex process in no

way necessarily precludes the invention of another method of selectively controlling a completely different region of the eye. Although the cited references are applied together, they must be first understood individually before drawing conclusions from their combination.

Turning first to the Brandt reference, even if it teaches the use of an inhibitor of a Na^+-K^+-$2Cl^-$ (symport), such as bumetanide, such use is irrelevant to Applicants' invention. This is because Dr. Civan and others have demonstrated that bumetanide is, by itself, ineffective in lowering IOP *in vivo*. See, attached, Tian *et al.* "Effects of Adenosine Agonists on Intraocular Pressure and Aqueous Humor Dynamics in Cynomolgus Monkeys," *Exp. Eye Res.* 64:979-989 (1997) (demonstrating that bumetanide had no effect on IOP of live monkeys). Subsequently, Dr. Civan and associates demonstrated that bumetanide also has no effect on IOP of the live mouse, and it lowers IOP only if the sodium-proton exchange is also blocked (see, attached 2002 Avila *et al.*, reference in *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902). Consequently, the attached references are used solely to establish the art as known at the time of the cited references.

As a result, when the cited prior art is read in light of the state of the art, although Brandt's patent may teach that use of bumetanide to block the sodium-potassium-chloride co-transporter, it clearly offers no suggestion of Applicants' process directed to the selective inhibition of sodium-proton exchange. Thus, Brandt has no relevance to Applicants' claimed method of selectively blocking of sodium-proton exchange, as confirmed by the Examiner's statement in the Office Action that Brandt "fails to suggest administration of selective NHE/NHE1 inhibitors."

However, in the Examiner's rejection, Brandt is not cited alone. It is combined with Cherksey. But, for the above stated reasons, Cherksey teaches a method for treating intraocular pressure by administering to affect the amiloride-sensitive sodium channel, but as established above, that is not Applicants' invention. In fact, Applicants' neither mention, nor consider, the role of the sodium channel in the instant patent application which focuses instead on regulation of aqueous humor formation. To the contrary, as explained above, Cherksey actually leads one away from Applicants' invention.

Consequently, linking treatment of bumetanide as an inhibitor of a Na^+-K^+-$2Cl^-$ (symport) (Brandt) with amiloride in a gel to block the ENaC sodium channel (Cherksey)

would in no way lead one of skill in the art to believe that the combination could selectively block sodium-proton exchange (which is suggested by neither component of the combined art, in order to reduce inflow at the sodium-hydrogen antiports within the ciliary epithelial cell layer. As a result, when the cited references are combined as proposed, the combination fails to teach each and every element of Applicants' claimed invention. Of course, as above, inherency does not apply to the combined references. See, *Jones v. Hardy* 220 USPQ 1020, 1025 (Fed. Cir. 1984) (The fact that a claimed invention is based on an inherent quality of a product well known in the art does not mean the invention is obvious, as this confuses anticipation by inherency with obviousness).

Since Cherksey fails to teach administering NHE/NHE1 inhibitors to the antiports, as taught for the first time by Applicants, Cherksey cannot supplement the gap left by Brandt. Consequently, the combination of Brandt and Cherksey still fails to render Applicants' invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 94-96, and 102 – 110, 112, 113 under 35 U.S.C. §103(a) be reconsidered and reversed, and the case moved to allowance.

In sum, therefore, Applicants believe that all rejections have been overcome, and the application is in condition for allowance. Accordingly, Applicants respectfully ask that the application be moved to allowance at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendment or response, please contact Applicants' undersigned representative at (215) 772-7550. Please direct all correspondence to the below-listed address. If there are any fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-4764.

Respectfully submitted,
Civan *et al.*

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By: Evelyn H. McConathy
Evelyn H. McConathy
Registration No. 35,279
Attorney for Applicants
MONTGOMERY, McCRACKEN,
WALKER & RHOADS, LLP
123 South Broad Street,
Philadelphia, PA 19109-1099
Tel: (215) 772.7550
Fax: (215) 772.7620

Attached:

1) Civan and Macknight, *Experimental Eye Research* 78(3):625-631 (March 2004).

2) Do and Civan, *Acta Physiologica* 187(1-2): 345-352 (May/June 2006).

3) Tian *et al.*," *Exp. Eye Res.* 64:979-989 (1997).

4) Avila *et al.*, *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902 (2002).